

# Accurate detection of coronary heart disease by new exercise test

M S ELAMIN, R BOYLE, M M KARDASH, D R SMITH, J B STOKER, W WHITAKER, D A S G MARY, R J LINDEN

*From the Department of Cardiovascular Studies, University of Leeds, and Departments of Medical Cardiology, Leeds General Infirmary and Killingbeck Hospitals, Leeds*

**SUMMARY** The ability of a new exercise test accurately to detect the presence and severity of coronary heart disease has been examined in 206 patients with anginal pain, including patients on beta blockers or with concomitant cardiac lesions. From recordings of 13 electrocardiographic leads during exercise, the maximal rate of progression of ST segment depression relative to increases in heart rate (maximal ST/HR slope) was obtained and used as an index of myocardial ischaemia. The maximal ST/HR slope and results of coronary arteriography were independently obtained and the two sets of data compared. The ranges of the maximal ST/HR slopes in the 38 patients with no significant disease, 49 with single vessel, 75 with double vessel, and 44 patients with triple vessel disease were different from each other and there was no overlap in the data between adjacent groups; there were no false positive, false negative, or indeterminate results. It is concluded that the maximal ST/HR slope can be used reliably to predict the presence or absence and severity of coronary heart disease in individual patients presenting with anginal pain in a hospital population.

In a recent preliminary study in 64 patients with anginal pain it was suggested that a new exercise electrocardiography test was able accurately to predict the presence and severity of coronary artery disease.<sup>1</sup> In that study the rate of progression of ST segment depression with respect to the increase in heart rate during exercise (the maximal ST/HR slope) was used as an index of myocardial ischaemia and an independent comparison with results of coronary arteriography showed complete agreement. The maximal ST/HR slopes and the coronary arteriographic findings in 64 patients<sup>1</sup> were independently obtained and documented to allow the comparison between the two sets of data to be made in a blind fashion.<sup>1</sup> There were 14 patients without significant coronary artery disease, 17 with single, 18 with double, and 15 with triple vessel disease; these arteriographic findings were successfully predicted by the maximal ST/HR slope and there were no false results.<sup>1</sup>

The present study was designed prospectively to examine a greater number of patients (142 patients) with anginal pain. The maximal ST/HR slope again predicted exactly, without false results, the presence or

absence and the number of significantly diseased coronary arteries as determined independently by angiocardiology; some of these results have previously been communicated to the British Cardiac Society.<sup>2</sup>

## Patients and methods

The 142 consecutive patients studied prospectively were selected on the basis of chest pain or classical angina and were proceeding to coronary arteriography; none of them had right bundle-branch block or was taking digoxin or nifedipine. Patients with unstable angina, heart failure, cardiac arrhythmias, or uncontrolled hypertension were not entered into the trial. Before entry to the trial it was decided also to exclude patients in whom left ventricular aneurysm was subsequently shown by left ventriculography, because previous reports have suggested that this condition results in elevation of the ST segment.<sup>3</sup> Patients with these diagnoses were excluded from the previous study,<sup>1</sup> as were those on beta blockers. Unlike the previous study, however, patients on beta blockers were included in this investigation as there was preliminary evidence that this treatment did not affect

the test.<sup>4</sup> The beta blocking agents used were metoprolol (30 patients), oxprenolol (22 patients), atenolol (four patients), and propranolol (four patients). Also excluded from the previous trial but included in this investigation were patients with cardiac lesions other than coronary artery disease. Such patients, diagnosed by echocardiography and/or cardiac catheterisation, were four with mitral valve disease, one of whom had a prolapsing mitral valve, four with mixed aortic valve disease, two with hypertrophic cardiomyopathy, one with hypertension and left ventricular hypertrophy, and three with left bundle-branch block.

#### EXERCISE TEST

The maximal ST/HR slope was independently obtained and compared with the results of coronary arteriography obtained within one week of the exercise test. The exercise test was performed in the upright position on a bicycle ergometer with the patient pedalling at 60 rpm against a continuous series of incremental loads. Though the details of the test have previously been described,<sup>1</sup> it is necessary to repeat the description with some amplification to detail to allow further explanation. Briefly, in each patient the test was preceded by a recording of the resting electrocardiogram in the supine position, and in the upright position on a bicycle ergometer before and during hyperventilation and during a short preliminary exercise to determine the increments in workload necessary to obtain increments in heart rate of about 10 beats a minute. After a suitable rest period (heart rate down within 5% of the previous control value) the workload was increased in these increments at three minute intervals to cause the increases in heart rate. The test was terminated for the following reasons: the presence of anginal pain, the occurrence of large ST segment depression of about 0.3 mV, the occurrence of more than six ventricular ectopic beats/min (multifocal or consecutive), a decrease in blood pressure, or exhaustion of the patient.

The electrocardiogram was recorded from 13 leads, 12 conventional leads and a bipolar lead (CM5), using a commercially available ink jet Mingograph recorder.<sup>15</sup> The leads were calibrated in the usual way by setting the amplifier gain so that a 1 mV signal caused a displacement of 10 mm. Records from the 13 electrocardiograph leads were obtained during the last minute of each exercise level, recorded before, during, and for at least five minutes after stopping the exercise. The electrocardiogram (from four leads at a time) and the heart rate were continuously displayed to monitor progress. In addition, the systemic blood pressure was measured, before, during the third minute of each level of exercise, and after exercise.<sup>1</sup>

Measurements were made on electrocardiograms

obtained during the steady state (heart rate value within  $\pm 5\%$  of mean) attained during the third minute of each level of exercise. The values of the heart rate and displacement of ST segment used in this study were taken as the average of values measured in at least 10 consecutive cardiac cycles and were obtained from records of all 13 electrocardiograph leads. The displacement of the ST segment was measured at a point 80 ms after the QRS complex, that is after the J point; the level of the line drawn between consecutive PR segments was taken as the zero reference. Measurement of the ST segment was made using a magnifying glass fitted with a graticule marked in 0.1 mm divisions. The heart rate (beats/min) was calculated by measuring the RR interval on the electrocardiogram.

Using the values of the depression of the ST segment below the zero reference and the heart rate during exercise the maximal ST/HR slope was derived. The values of displacements of ST segment and heart rate were analysed, in each of the 13 leads, to yield a curve relating the values of the ST segment as the dependent variable to the values of heart rate as the independent variable during rest and exercise. The rate of development of ST segment depression with respect to the increments in heart rate, observed in any lead, was represented by the slope of a computed regression line. This line was obtained from points on the curve which, during submaximal exercise, showed a linear regression of ST segment on heart rate as indicated by a value of correlation coefficient which was statistically significant. The steepest slope of ST/HR relation in each lead was obtained by comparing the slope of the final three points on the curve with that obtained by progressively including further points at submaximal levels of exercise. Considering all recorded electrocardiographic leads, the maximal ST/HR slope obtained in each patient during the exercise test indicated the maximum rate of development of ST segment depression with respect to the increase in the heart rate. This slope represents the steepest slope of all the regression lines which show a linear relation (between the heart rate and the ST segments), obtained from the 13 electrocardiographic leads.

For the purpose of comparing the maximal ST/HR slopes obtained from one group of patients with values obtained from any other, first, the means of the groups of the maximal ST/HR slopes were analysed using Student's *t* test for unpaired samples. Secondly, regression analysis was performed on pooled data of the changes in the level of ST segment and heart rate in each group. The slope of those pooled regression lines was labelled the maximal  $\Delta\text{ST}/\Delta\text{HR}$  slope.

In addition, to aid comparison of our group of patients with other groups in which the other usual exercise tests had been completed, in each patient the maximal heart rate, the maximal ST segment

depression, and the product of heart rate and systolic blood pressure attained during exercise were measured. The outcome of these exercise tests was assigned to either of three categories, positive test, negative test, and indeterminate test as previously described.<sup>5</sup> A test was positive when a net ST segment depression greater than 1 mm was recorded in any of the 13 leads of the electrocardiogram, negative when the patient attained a value of heart rate of greater than 85% of age predicted maximal heart rate response without much ST depression, and indeterminate when exercise had to be terminated for reasons other than those indicating a positive or a negative test result.

#### ANGIOCARDIOGRAPHY

In each patient, within a week of the exercise test, selective coronary arteriography and left ventriculography were performed and reported on by the consultant cardiologists without knowledge of the results of exercise. Significant coronary artery disease was defined as luminal narrowing of the diameter of greater than 75% in any of the three major coronary arteries as previously described.<sup>1</sup> Patients were divided

into four groups, those with no significant coronary artery disease and those with single, double, and triple vessel disease. Significant narrowing of the left main coronary artery was considered to be equivalent to significant narrowing of its two major branches and labelled double vessel disease.<sup>1</sup>

#### Results

##### MAXIMAL ST/HR SLOPE

An example of results in one patient is shown in Fig. 1. The ranges of the maximal ST/HR slope of the four groups in the prospective study (142 patients), whether or not they were on beta blockers or had cardiac lesions other than coronary artery disease, are all within the ranges determined from the group of 64 patients from which results have been previously reported,<sup>1</sup> as shown in Table 1. Therefore the data from all patients have been pooled. The ranges of the maximal ST/HR slopes in the four groups of patients, that is those with no significant coronary artery disease, single, double, and triple vessel disease, are different from each other and there is no overlap between the ranges of adjacent groups. The differences between the maximal ST/HR slope of one group and any other were statistically significant ( $p < 0.0005$ ).

The pooled data for the four groups of the 206 patients (that is including both the previous group of 64 and the prospective group of 142 patients) are shown in Fig. 2. The maximal  $\Delta ST/\Delta HR$  slopes are significantly different ( $p < 0.05$ ) from each other.

##### CLINICAL DETAILS

The clinical and angiographic details of the 206 patients are shown in Table 2. Their mean age was 47.6 years  $\pm 0.68$  (mean  $\pm$  SEM). A history of documented myocardial infarction at least six months before the exercise test was present in 37 (18%) of the patients. In 38 patients (18%) there was no significant coronary artery disease. In 16 of these patients the coronary arteries were normal; in the remainder, luminal narrowing of the coronary arteries amounted to 25% (mean: range 10 to 50). Significant coronary artery disease in at least one vessel was observed in 168 patients (82%); in these patients the reduction in the lumen of the vessels was 89.6% (mean: range 75 to 100). Of these 168 patients, 124 had one or two vessel disease and, of these, 61 had no additional coronary lesions; the remainder (63 patients) had reductions in the lumen of other vessels of 26.9% (mean: range 10 to 50). It is apparent from the results of coronary arteriography that no major vessel was seen to be narrowed to an extent greater than 50% and less than 75%. We have no explanation of this phenomenon which, however, may be related to the rates of progress of the disease as explained in the discussion, or, alterna-

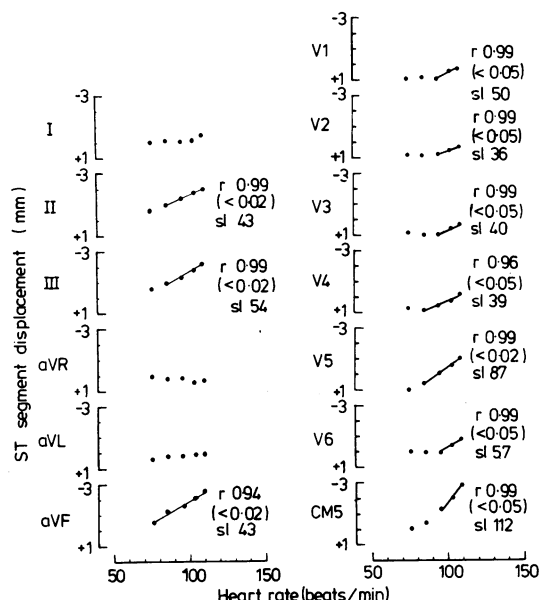


Fig. 1. An example of the relation between the level of the ST segment and the heart rate (HR) in each of the 13 electrocardiographic leads obtained during exercise in one patient. The continuous lines are the steepest of the computed regression lines which show a linear ST/HR relation; the correlation coefficient ( $r$ ) and  $p$  value are shown in relation to these computed lines;  $Sl$  is the slope of the computed regression line in mml beats per min per 1000. The patient was shown by selective coronary arteriography to have triple vessel disease.

Table 1 Maximal ST/HR slope, expressed as range (mean), in 142 patients compared with values of maximal ST/HR slope obtained in preliminary study of 64 patients.<sup>1</sup>

Angiographic classification		No significant disease	Single vessel disease	Double vessel disease	Triple vessel disease	Total No. of patients
Preliminary trial <sup>1</sup>	No. of patients	14	17	18	15	64
	Maximal ST/HR slope*	3-11 (9)	13-21 (18.1)	32-59 (45.6)	69-137 (88.1)	
Prospective trial	No. of patients	24	32	57	29	142
	Maximal ST/HR slope*	3-11 (8.9)	13-21 (18.5)	32-59 (44.2)	69-122 (86.9)	
Total	No. of patients	38	49	75	44	206
	Maximal ST/HR slope*	3-11 (8.9)	13-21 (18.4)	32-59 (44.5)	69-137 (87.3)	

\*mm beats per min per 1000.

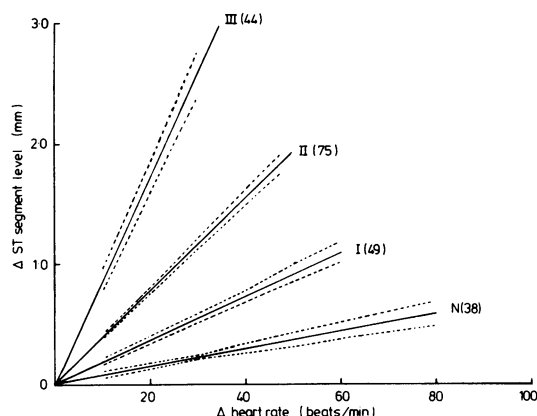


Fig. 2. Pooled data of the relation during exercise between changes in the level of the ST segment ( $\Delta$ ST) and changes in heart rate ( $\Delta$ HR) in the four groups of patients; no significant coronary artery disease (N), single vessel disease (I), double vessel disease (II), and triple vessel disease (III). The continuous lines are the computed regression line of  $\Delta$ ST/ $\Delta$ HR relation for each of the four groups and the interrupted lines indicate the 95% confidence limits of the data in each group.

tively, to the interpretation of the arteriograms. Though the coronary arteriograms were assessed by the consultant cardiologists in group discussion the joint decision may have resulted in a bias towards "all or none" decisions, that is significant constriction (>75%) or insignificant constriction (50% or less). To test these hypotheses further, evidence from greater numbers would have to be obtained. It should still be stressed, however, that the results of coronary angiography were independently obtained in this blind study by staff not associated with the exercise study.

Of the 14 patients with concomitant cardiac lesions, as mentioned in the Methods section, only three had coronary artery constriction of greater than 75%—two patients with left bundle-branch block and one with hypertension. A dominant left coronary artery system was observed in 16% of patients with no significant coronary artery disease, 8% of those with single vessel disease, 11% with double vessel disease, and 21% with triple vessel disease. Significant left main stem stenosis was found in five of the 75 patients with double vessel disease and in 11 of the 44 patients with triple vessel disease.

Table 2 Angiographic and clinical details of 206 patients

Group	Sex M	F	Age years range (mean)	History of previous myocardial infarction	Slight to moderate hypokinesia of left ventricle
<i>Patients without beta blockers</i>					
No significant disease	16	9	27-62 (40.9)	—	—
Single vessel disease	29	8	26-63 (46.8)	5	5
Double vessel disease	37	4	26-64 (48.1)	12	16
Triple vessel disease	29	—	33-64 (48.4)	10	16
<i>Patients with beta blockers</i>					
No significant disease	—	2	53, 54	—	—
Single vessel disease	9	—	37-63 (51.8)	2	1
Double vessel disease	31	3	40-61 (50.7)	4	4
Triple vessel disease	15	—	31-57 (46.1)	4	5
<i>Patients with concomitant cardiac lesions</i>					
No significant disease	8	3	16-58 (48.1)	—	—
Single vessel disease	3	—	45-56 (49.7)	—	—
Total	177	29	16-64 (47.6)	37	47

## OTHER EXERCISE TESTS

Other standard exercise test criteria obtained from these results did not differentiate the four groups successfully. There was a pronounced overlap in the maximal ST segment depression, heart rate, and rate pressure product attained during exercise between the four groups of patients. These criteria did not identify the presence or extent of coronary artery disease in individual patients. The results of using the usual criterion of ST segment depression of greater than 1 mm at the end point of the test in these 206 patients are as follows. In 60 patients (29%) indeterminate tests were obtained (Table 3); none of these patients, in the absence of ST segment depression of 1 mm, attained 85% of their age predicted maximal heart rate change. Of the remaining 146 patients, 129 had significant coronary artery disease and 17 did not and their details are shown in Table 4. Of the patients with coronary artery disease, 120 had positive test results (ST segment depression greater than 1 mm); the sensitivity was 93% (120/129). Of the 17 patients without significant coronary artery disease, 15 had negative test results, that is they attained greater than 85% of their age predicted maximal heart rate change; the specificity was 88% (15/17). Of the 122 patients with positive test results, 120 had significant coronary artery disease; the true positive rate was 98% and the false positive rate was 2%. Of the 24 patients with negative test results, 15 had no significant coronary artery disease; the true negative rate was 62% and the false negative rate was 38%.

## ACCURACY OF MEASUREMENTS

The ability of the observer to discriminate small displacements of the ST segment was assessed separately. The same record was analysed weekly by the observer;

these additional records were interspersed among other similar records by an independent person.

The differences in 10 consecutive measurements of the level of ST segment in the same trace ranged from  $-0.05$  to  $+0.05$  mm. The 95% tolerance limits with 95% confidence of the deviations of the measurement from the mean was 0.11 mm.

## OVERALL REPRODUCIBILITY OF TEST RESULTS

The exercise was performed twice within seven days in each of 37 patients. There were five patients with no significant coronary artery disease, nine with single vessel disease, 16 with double vessel disease, and seven patients with triple vessel disease. The differences in the pooled data of the maximal  $\Delta\text{ST}/\Delta\text{HR}$  slope between the repeated measurements in these patients were not statistically significant ( $p>0.5$ ). The 95% tolerance limits, with 95% confidence, of the differences in the maximal ST/HR slope was 0.71 mm/beat per min per 1000; this value amounts to 1.7% of the mean maximal ST/HR slope of 42.2 mm/beat per min per 1000 in the 37 patients.

In contrast, in the same 37 patients, the 95% tolerance limits, with 95% confidence of the differences in the maximal ST segment depression, heart rate, or rate pressure product, respectively, were 0.30 mm (25.6%), 40.1 beats per min (32%), and 6.2 kPa/min per 100 (28%).

## Discussion

## ABSENCE OF FALSE RESULTS

Using the maximal ST/HR slope in the present population under study, which included patients on beta blockers or with additional cardiac lesions, there were no false negative or false positive results; that is 100% agreement between the maximal ST/HR slope and the results of coronary arteriography. Explanations for this complete agreement are considered later together with an explanation of the absence of overlap between the ranges of adjacent groups of ST/HR slopes.

The usual criteria used in exercise tests are known to lead to some false results<sup>1,3,6</sup>; in patients with angina, having a prevalence of coronary artery disease of greater than 70% (coronary stenosis  $>70\%$ ), they are associated with a false negative rate of 15 to 45% and a false positive rate of 0 to 12%.<sup>5,7-11</sup> Moreover, beta blockers have been said to reduce the magnitude of ST

Table 3 Incidence of indeterminate test results in 206 patients using usual exercise test criteria

Group	No. of patients	Indeterminate results No. (%)
Patients without beta blockers	132	29 (22%)
Patients with beta blockers	60	21 (35%)
Patients with concomitant cardiac lesions	14	10 (71%)

Table 4 Accuracy (sensitivity and specificity) and true positive and negative test results in 146 patients using usual exercise test indices

	No. of patients	Sensitivity (%)	Specificity (%)	True rates Positive %	Negative %
Patients with coronary artery disease	129	93	—	98	—
Patients without coronary artery disease	17	—	88	—	62

segment depression<sup>12</sup> and to cause false negative results.<sup>3 6 13</sup> In addition, it has been shown that left bundle-branch block, hypertrophic cardiomyopathy, left ventricular hypertrophy, or valvar disease can cause false results.<sup>3 6 14-16</sup>

These false results are basically a result of the overlap in the ranges of data between patients with coronary heart disease and those without. This overlap in data could be attributed first to the fact that, in the usual exercise test, the test criteria are measured at a reference point in time which is subjectively determined. The variability, represented by the 95% tolerance limits, of estimating the usual test criterion (1 mm ST segment depression) in the patients in the present study amounts to  $\pm 26\%$ , and is similar to those previously reported.<sup>17 18</sup> Secondly, ST segment depression *per se* could be effected during exercise by conditions other than coronary heart disease, for example hyperventilation, therapeutic agents, or the presence of concomitant cardiac lesions.<sup>3 6</sup>

#### PREDICTIONS OF CORONARY ARTERY DISEASE FROM NEW TEST

The results from an examination of 206 patients show that the maximal ST/HR slope can be used accurately to predict the presence or absence and the severity of coronary artery disease in individual patients with anginal pain. Such a conclusion is based on the following facts. First, no indeterminate results were obtained using the maximal ST/HR slope. A definitive test result was obtained in each of the 206 patients irrespective of whether or not the patient had achieved 85 to 100% of the age predicted heart rate change during exercise. Secondly, the ranges in the four groups of patients, those with no significant disease, with single, double, and triple vessel disease, were different from each other and there was no overlap between the groups; the differences between the ranges exceeded the tolerance limits of the measurement. In the 206 patients, the maximal ST/HR slope corresponded each time with the results of coronary arteriography, and there were no false results.

The fact that there were 206 successful agreements without an error in this comparison between the maximal ST/HR slope and the results of coronary arteriography, independently obtained in 206 patients, allows the maximal ST/HR slope to predict with a confidence of 99% the presence or absence of significant coronary artery disease in at least 97.8% of patients with angina (see Appendix).

#### ADVANTAGES OF MAXIMAL ST/HR SLOPE

There are several advantages in the use of this test. Many patients presenting with angina are already on beta blockers; the fact that the results of the test were the same whether the patients were on beta blockers or

not (also see<sup>4</sup>) means that these need not be stopped. In addition, it is possible that patients with the additional cardiac lesions similar to those encountered in this study will also be able to be examined. Further studies, however, with larger numbers are required to establish statistically whether measurement of the maximal ST/HR slope in patients with such cardiac lesions will still allow accurate prediction of the presence and severity of coronary heart disease in them.

Accepting that the maximal ST/HR slope is an accurate index of coronary artery disease, the use of the slope in the clinical management of patients with coronary heart disease can now be considered. First, of the patients attending hospital for coronary arteriography because of anginal pain, up to 30% or more have no significant coronary artery disease<sup>8 11 19-21</sup> (18% of the patients in this investigation) and the maximal ST/HR slope could be used to identify them. Secondly, of the patients with coronary artery disease, single vessel disease was present in 26% of the patients presenting with angina; in some other studies the incidence of single vessel disease ranged from 20 to 45%.<sup>5 8 11</sup> The use of the usual exercise criteria has been shown to result in an incidence of false negative results which is higher in patients with single vessel disease than in those with multi vessel disease<sup>5 11 22</sup> and, from evidence in this report, cannot be used to identify the severity of coronary artery disease in individual patients. The maximal ST/HR slope, however, enables the accurate diagnosis of a single significantly diseased coronary vessel. This allows the clinician to avoid or delay coronary arteriography in this group also, subject to the responses of the patient to treatment.

Thirdly, it has been reported that the mortality rate in this disease is favourably affected by aortocoronary bypass, in comparison with medical treatment, only in patients with multivessel disease.<sup>23</sup> Therefore, by using the maximal ST/HR slope to predict significant coronary artery disease it becomes possible to perform coronary arteriography *only* in those patients in whom the test indicates multivessel disease, that is only in those patients where surgery would be contemplated on grounds other than a failure of medical treatment. It is even possible that coronary arteriography would be performed early in these patients without waiting for such a failure. With reference to the patients with significant left main stem stenosis there are inadequate numbers to analyse with a view to separating them from the groups with double vessel or triple vessel disease. In practice, as all the patients with double or triple vessel disease will probably proceed to coronary arteriography, these patients are not likely to be missed. As a corollary of this use the maximal ST/HR slope could be used functionally and non-invasively to assess the results of aortocoronary bypass or percutaneous coronary angioplasty and serially in follow up to predict,

for example, graft occlusion or deterioration of coronary artery disease.

Therefore, the use of maximal ST/HR slope in those with symptoms enables the number of patients undergoing coronary arteriography, with its attendant mortality and morbidity,<sup>24</sup> to be reduced to a necessary minimum. At the very least, approximately 30% of those who on present criteria undergo coronary arteriography need not be subjected to this invasive technique. In addition, the exercise test is clearly less expensive in terms of consumables and capital expenditure and less time consuming overall.

Subjects without symptoms may have significant coronary artery disease—even triple vessel disease.<sup>25, 26</sup> It could be argued that a non-invasive test which is as successful in predicting coronary artery disease as this could be used in such populations to discover those subjects whose cardiological condition could affect the welfare of the public, for example aeroplane pilots.

#### DISADVANTAGES OF NEW TEST

So far, however, the general use of the new test is limited because the test is time consuming; though the actual test takes less than half an hour, the measurement of records and calculation of the maximal ST/HR slope for each patient takes about three hours. At present a computer program, using a dedicated small microprocessor, is being examined by comparing the ST/HR slopes obtained by the computer with those obtained manually from the electrocardiograph records. When these results are available the usefulness of the test should be enhanced.

#### POSSIBLE EXPLANATION OF RESULTS

##### *Linear ST/HR relation*

The basis of the ST/HR slope must reside in the relation between the oxygen consumption of the heart and the heart rate, the latter being a main determinant of oxygen consumption.<sup>27</sup> Thus, there is evidence of a linear relation between myocardial oxygen consumption and increases in heart rate whether this is brought about by pacing the heart or by exercise.<sup>28–31</sup> Further, with a restricted inflow of blood to a major coronary vessel, that is a restricted supply of oxygen, increases in the heart rate should cause a progressively increasing degree of ischaemia. It has been shown that there is a linear correlation between the magnitude of ST segment displacement obtained from epicardial maps and increases in heart rate in anaesthetised dogs with an occluded coronary artery.<sup>32</sup> In dogs in whom coronary arteries have been constricted slowly over a period of time it has been shown that the normal increases in myocardial blood flow are drastically reduced in the subendocardial region supplied by the occluded arteries and that this reduction is dependent not only on the coronary perfusion pressure but also on the increases in

heart rate and in local extravascular coronary resistance in association with augmented left ventricular end-diastolic pressure.<sup>33–36</sup> Several studies have shown that the degree of ST segment displacement correlates with the severity of reduction in myocardial blood flow<sup>37–40</sup> and with the degree of reduction in myocardial oxygen tension.<sup>41–43</sup> Thus, from this evidence there *should* be some relation between ST segment depression, representing the degree of ischaemia (or lowered blood flow and oxygen tension) and heart rate; and the relation should be roughly linear. In the event, the ST/HR slope was surprisingly linear, that is the confidence limits around the regression lines were very small (see Fig. 1, Elamin *et al.*<sup>1</sup>). The ST/HR slope could represent an index of the balance between increases in myocardial oxygen consumption and the limitations on blood supply, and therefore possibly an index of ischaemia.

##### *Ranges of maximal ST/HR slope*

One remarkable finding in the present investigation is that adjacent ranges of the maximal ST/HR slopes, each range correlating with insignificant, single, double, or triple vessel disease, have shown no overlap; the limits of adjacent ranges are quite separate. One reason is that the data are presented in relative terms rather than absolute. Though absolute values are measured, plotted, and used in the calculations, no relevance is attached to the resting condition; only the *changes* in the HR and ST segment depression can be discerned in the value of the slope which is expressed as a rate of change.<sup>1</sup> The fact that there is only a very small variation in deriving each maximal ST/HR slope, that is the 95% tolerance limits were  $\pm 1.7\%$ , prevents any masking of biological differences in the assessment of the severity of myocardial ischaemia and allows the recognition of no overlap in the present data. The tolerance limits are remarkably narrow because during the primary measurements the random errors are averaged and therefore mainly disappear; “averaging” occurs three times in the calculation. First, there is a steady state of heart rate and electrocardiograph record, and the heart rate has a very small variance. Secondly, the measurements from at least 10 consecutive cardiac cycles are averaged to provide a single measurement of heart rate or ST segment depression, leading to one point. Thirdly, several (three to six) points are used in determining a regression line; thus random error is again removed, as it is only the slope of the computed regression line which is used as the index.

How is it then that there is a “step change” from no significant coronary artery disease to single, from single to double, and from double to triple vessel disease? It is possible to postulate that in all three vessels the disease causing the reduction in the lumen occurs in each vessel but progresses at different rates in each<sup>44</sup>; thus

the emergence of 70% constriction in each vessel will occur at different times. Accepting laminar flow within the vessels, then, given the same pressure head, the flow is inversely related to the fourth power of the radius. A simple plot of the relation between flow and radius would show a very sharp sudden inflection. In terms of restriction of flow it is suggested that the progressive restriction occurs with time so that the period spent "at the inflection" is relatively short. The chances of doing an exercise test and finding someone with one of these vessels constricted such that the flow is at the inflection of the relation between constriction and flow, that is between adequacy (less than 75% constriction) and inadequacy (greater than 75% constriction) are very small. Thus, in time units of months during which this small change occurs, there is little chance of observing any patient with a vessel in this position. Obviously as the disease progresses in all vessels at the same time there will be successive changes from adequacy to inadequacy in the first, second, and third vessels independently. What should be interesting is to follow up our patients with successive tests at close intervals to see if we can recognise the progression through the sudden change from adequacy to inadequacy.

There is much support for the above hypothesis in that many studies have reported sudden decreases in flow in vessels showing about a 70% constriction. For example, the relation between flow and perfusion pressure was studied *in vitro* in proximal segments of coronary arteries having variable degrees of occlusion, and obtained from fresh postmortem hearts.<sup>45</sup> In that study, it was shown that a very small decrease in the luminal diameter in the range beyond 70% constriction resulted in a dramatic sudden reduction in blood flow, which was very much greater than that occurring when the increase in constriction was in the range from 0 to 70%; these results were explained using the pressure/flow relation known to exist in vessels exhibiting laminar or non-laminar flow<sup>45</sup> as suggested above as a basis for the present hypothesis. In addition, using *in vivo* measurements of vessel constriction and the pressure/flow relation of laminar and non-laminar flow it has been estimated that the decrease in flow becomes steeper and the pressure gradient doubles across constrictions which reduce the luminal diameter more than 60 to 75%.<sup>46</sup> During aortocoronary bypass only reductions (observed at coronary arteriography) in coronary diameter of greater than 80% cause large increases in the pressure gradient or reductions in myocardial blood flow.<sup>47</sup> Similar conclusions have been derived from experimental studies measuring coronary blood flow and involving constriction of coronary vessels in anaesthetised dogs; observations were made during control periods and during periods of reactive hyperaemia.<sup>48 49</sup>

An additional cause of sudden reduction in flow over time can be suggested if the coronary blood flow is regulated, at least partly, by a "water fall mechanism".<sup>36</sup> Increases in tissue pressure, especially in the subendocardial layers of the myocardium, caused by distension of the left ventricle during diastole, could result in increases in the pressure in small coronary vessels, thus leading to a reduction in the perfusion pressure head.<sup>36</sup> Again small decreases in upstream pressure caused by progressive constriction would allow sudden collapse of the downstream vessels at the same or similar high tissue pressures.

It is possible that the index, maximal ST/HR slope, gives some estimate of ischaemia effected by restriction of flow *however caused*, that is by constriction of the coronary artery, compression of supply vessels or exchange vessels (venules and capillaries); the latter would be effected by a high left ventricular end-diastolic pressure or an increase in the diameter of the ventricle. If this is so, then a further examination of the multiple slopes in any one patient should be more rewarding than studying just the maximal ST/HR slope, as has been done in this investigation. An analysis of the pattern of the slopes obtained from various electrocardiographic leads across the chest may indicate the degree of myocardial ischaemia. Such an analysis might be helpful in the group of patients without significant coronary artery disease, to attempt to dissociate the slopes in patients having coronary disease of less than an equivalent of one vessel from those in patients showing no coronary artery disease at all. Such a hypothesis cannot be tested, however, until the number of patients in the subgroups is adequate for statistical analysis.

If this postulate is true then we should be able to find patients with large hearts (high wall tension), high left ventricular end-diastolic pressure, but with no significant coronary artery disease, who during this new exercise test exhibit slopes indicating a degree of myocardial ischaemia. So far we have not found such a patient.

At present, all that can be concluded is that the maximal ST/HR slope is an accurate index of myocardial ischaemia and can be used reliably to predict the presence and severity of coronary heart disease in hospital patients with angina.

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Requests for reprints to Professor R J Linden, Department of Cardiovascular Studies, University of Leeds, Leeds LS2 9JT.

## Appendix

In the comparison between the maximal ST/HR slopes and the results of coronary arteriography, two complementary events could hypothetically ensue; first, *successful events*, when the maximal ST/HR slope agrees with arteriographic findings and, secondly, *unsuccessful events* when the maximal ST/HR slope fails to agree with the arteriographic findings.

Using the confidence limits of the binomial distribution, the rate of the successful events could be predicted, with assumed confidence limits, from the number of the two complementary events in a finite number of comparisons according to the following binomial formulation.

For confidence limits of 99% (single sided)

$$\sum_{k=0}^N (p)^{(n-k)} (1-p)^k \cdot C_k^n = 0.01^1$$

Where  $p$  is the probability of a successful event occurring  
 $n$  number of comparisons  
 $k$  number of unsuccessful events  
 $N$  maximal number of unsuccessful events required to satisfy the equality

$C_k^n$  number of combinations of arranging  $k$  unsuccessful events in  $n$  comparisons.

With no unsuccessful events, the binomial formulation, with 99% confidence limits, reduces to  $(p)^n = 0.01$  for single sided limits

$$\text{or } p = (0.01)^{\frac{1}{n}}$$

Therefore, with a 99% confidence limit, it could be predicted that when  $n=206$  and  $k=0$ , the probability of successful events ( $p$ ) would be 97.8%; when  $n=228$  and  $k=0$ , ( $p$ ) would be 98% and for  $n=458$  and  $k=0$ , would be 99%.

DAVID CLAYDEN

Department of Community Medicine and General Practice  
 Leeds University

DAVID MARY

Department of Cardiovascular Studies  
 Leeds University

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